PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PV/448/PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/CZ2005/000010	International filing date *(day/month/year)* 03.02.2005	Priority date *(day/month/year)* 05.02.2004
International Patent Classification (IPC) or national classification and IPC INV. C07C303/40		
Applicant ZENTIVA, A.S.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 5 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.12.2005	20.04.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Grammenoudi, S Telephone No. +49 89 2399-8324

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CZ2005/000010

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1, 2, 4-8, 10-14	as originally filed
3, 9	received on 06.12.2005 with letter of 01.12.2005

Claims, Numbers

1-10	received on 06.12.2005 with letter of 01.12.2005

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CZ2005/000010

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

D1= EP-A-0 257 787

1. The present application relates to a process for producing (R)-(-)-5-(2-aminopro-pyl)-2-methoxybenzenesulfonamide.

2. Document D1 cited on page 3, line 2, page 4, line 28 and page 10, lines 1 and 11 is considered to represent the closest state of the art. It discloses a process for producing (R)-(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide which compri-ses reacting 5-acetonyl-2-methoxybenzenesulfonamide with R-(+)-α-methylben-zylamine to obtain 2R,1R-2-methoxy-5-[2-(1-methylbenzylamino)propyl]benzene-sulfonamide hydrochloride, hydrogenating the latter to (R)-(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide hydrochloride whereupon this salt is converted to (R)-(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide (see D1, Examples 1-3). The problem to be solved by the present application with respect to the cited prior art is to provide an alternative process for the same purpose.

3. The process according to present claim 1 differs from the known method in that it starts with the amine of formula VIII which is subsequently N-acylated, chlorosul-fonated, hydrogenated and deacylated to produce (R)-(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide. There is no suggestion of such a process in the state of the art.

   Accordingly, the subject-matter of claim 1 meets the requirements of Article 33(2) and (3) PCT.

4. The compounds of claim 9 are novel and serve as intermediates in the process according to claim 1. Thus, the subject-matter of claim 9 meets the requirements of Article 33(2) and (3) PCT.

5. Dependent claims 1-8 and 10 concern particular embodiments of claims 1 and 9 respectively. They fulfil the requirements of Art. 33(2) and (3) PCT as well.

SECTION VIII

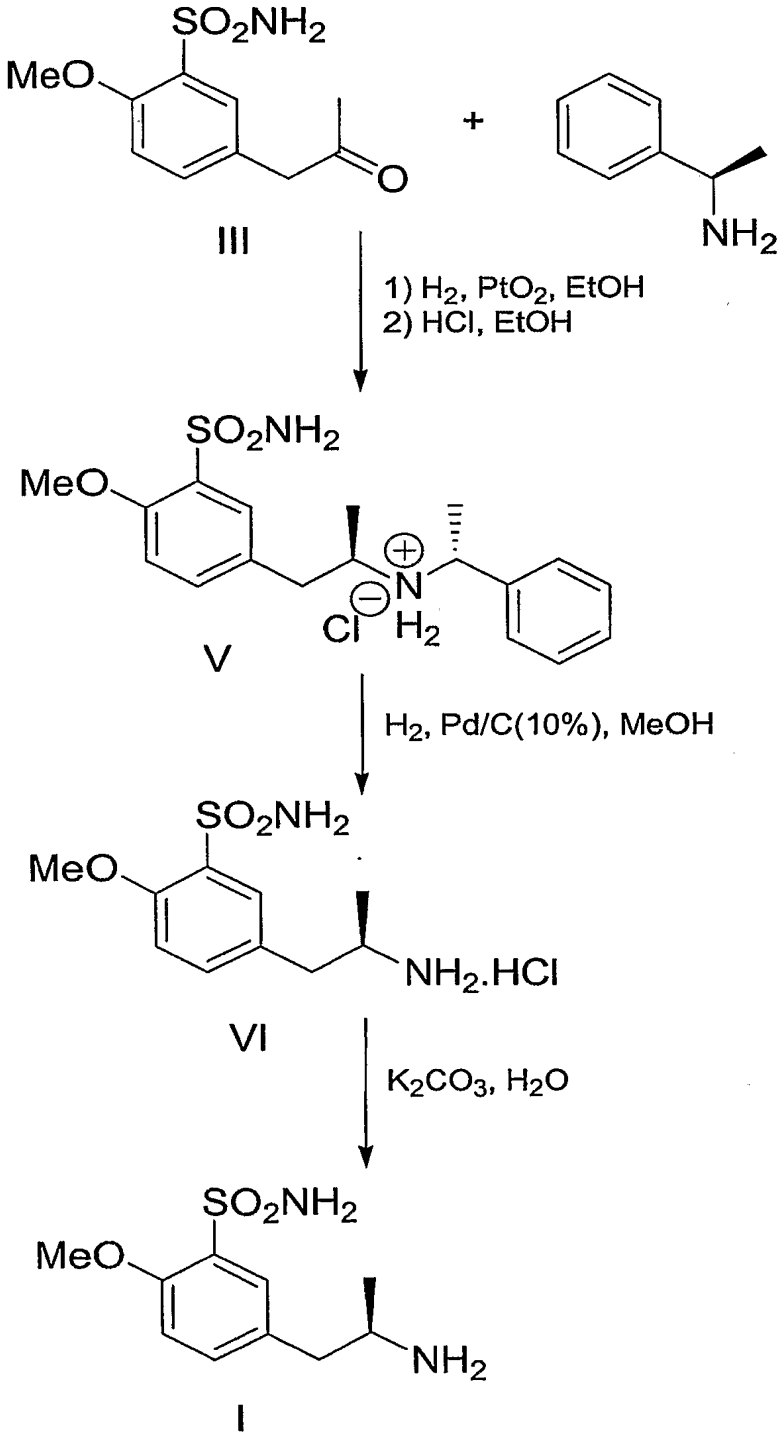
1. The feature "50-100°C" of claim 3 is not supported by the description (cf. page 5, lines 11-12) as required by Article 6 PCT.

2. The number "VII" on page 9, line 4 and page 12, line 6 as well as the formula of R-(+)-α-methylbenzylamine depicted on page 10, first reaction scheme (cf. Exam-ple 6, 2.1) are obviously incorrect (Art. 6 PCT).

3. The two-step chlorosulfonation reaction scheme on page 9 as originally filed has been replaced by the hydrogenation reaction scheme depicted on page 10, lines 1-5 (with a corrected formula of R-(+)-α-methylbenzylamine). As a result, the description of the prior art method for producing tamsulosin now comprises two hydrogenations on platinum wherein, however, the compound numbering (VII and III) as well as the yield data (40%, 74% and 30%) of the first hydrogenation step from the chlorosulfonation. This inconsistency within Example 6 renders it unclear, contrary to the requirements of Article 6 PCT.

The synthesis turned out to be very advantageous if the starting amine I was prepared according to the method described in patent EP 257787, or divisional EP 380144.

The patents describe the path indicated in the following scheme:



Example 5

Preparation of (R)-(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide I

Intermediate VII (10.5 g) is boiled in 5% HCl (250 ml) under a reflux condenser for 16 to 18 h. The course of the reaction is controlled with TLC detecting the starting substance. After the reaction is complete, the reaction mixture is concentrated to about 1/3 of its volume, then, a saturated solution of sodium carbonate (50 ml) is slowly added dropwise under stirring. After the addition, pH~10 is controlled and the reaction mixture is stirred for 0.5 hour, then let to crystallize at 0 °C. The precipitated crystals are sucked off and the filtrate is concentrated to ½ of its volume and let to crystallize at 0 °C. Both fractions (4 g + 8 g) of white to brownish crystals are combined and re-crystallized from water. The yield is 7.52 g (80 %).
^{1}H NMR: δ 0.99(d, J=6.2, 3H,C<u>H</u>$_3$); 2.54(dd, J=13.6 J=6,8, 1H, C<u>H</u>$_2$); 2.59 (dd, J=13.6; J= 6.7; 1H, C<u>H</u>$_2$); 3.00(sex, J=6.4; 1H, C<u>H</u>); 3.53(bs, N<u>H</u>$_2$); 3.92(s, 3H, C<u>H</u>$_3$O); 7.16(d, J=8.4; 1H, C<u>H</u>$_{arom}$); 7.41(dd, J=8.4; J= 2.2; 1H, C<u>H</u>$_{arom}$); 7.59(d, J=2.2; 1H, C<u>H</u>$_{arom}$). (CD_3SOCD_3, 30 °C)

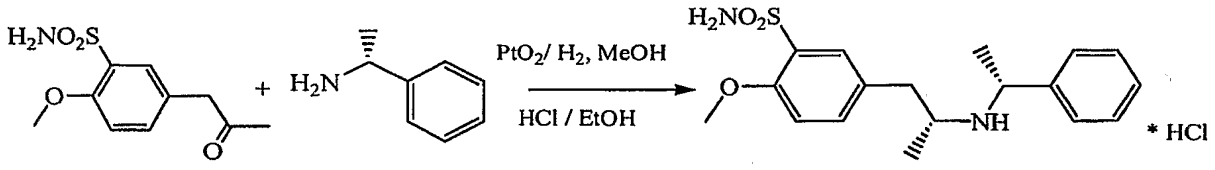
Example 6 - comparative

A method of preparation of tamsulosin (II) according to the prior art in comparison with the method with included steps according to the invention

1. The method according to the prior art

1.1. Chlorosulfonation in two steps according to US 4,731,478 (1988)

1.2.

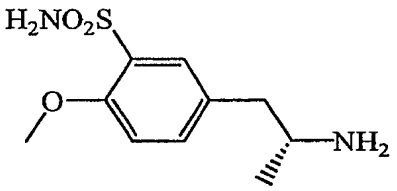


VII **yield 40%** **yield 74%** III

total yield 30%

C L A I M S

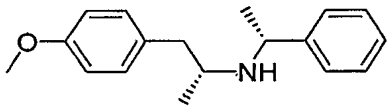
1. A method of preparation of (R)-(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide of formula I



I

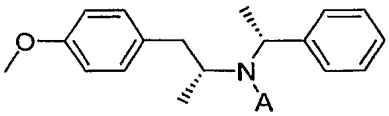
characterized in that

a. a protecting group is introduced to N-[(1R)-2-(4-methoxyphenyl)-1-methylethyl]-N-[(1R)-1-phenylethyl)]amine of formula VIII



VIII

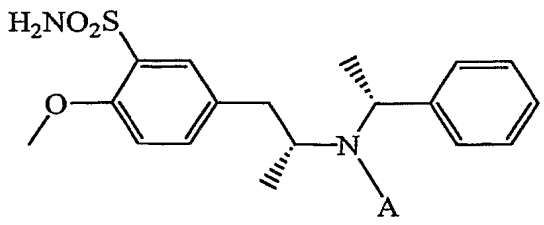
to obtain an amide of formula IX



IX,

wherein A can be an acyl having 2 to 8 carbons,

b. whereupon the amide of formula IX is chlorosulfonated and the resulting sulfochloride is converted to a sulfonamide of formula X



X

wherein A is as defined above,

c. and the sulfonamide of formula X is hydrogenated and deacylated to obtain the compound of formula I.

2. The method according to claim 1 characterized in that the protecting group A is an acyl, preferably acetyl.

3. The method according to claim 2 characterized in that acetanhydride at 50 to 100 °C is used as the acetylation agent.

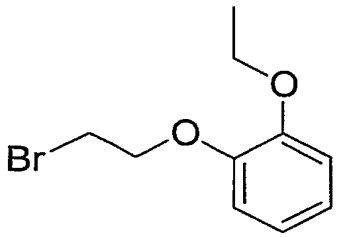
4. The method according to claim 1 characterized in that the sulfochloride resulting from chlorosulfonation is not isolated and is directly converted to the sulfonamide with ammonia.

5. The method according to claim 4 characterized in that chlorosulfonation takes place in methylenechloride at –30 to +30 °C.

6. The method according to claim 1 characterized in that hydrogenation is carried out under catalysis with palladium.

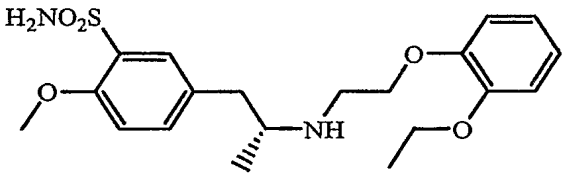
7. The method according to claim 6 characterized in that the catalyst is 3% Pd/C with 50% water content at a pressure of 2 MPa and a temperature of 80 to 85 °C.

8. The method according to claim 1, characterized in that the product of formula I is further reacted with a compound of formula IV



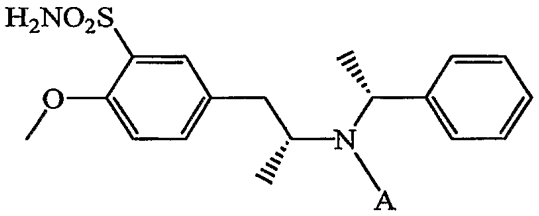
IV

to form the final product of formula II



II

9. A sulfonamide of formula X



X

wherein A is as defined in claim 1.

10. The sulfonamide according to claim 9, wherein A is acetyl.